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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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WENDEROTH, LIND & PONACK, L.L.P.
2033 K STREET N. W.
SUITE 800
WASHINGTON, DC 20006-1021

EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,598	YAMANE, AKIO	
	Examiner	Art Unit	
	Sally A. Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/9/2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/18/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is written in response to applicant's correspondence submitted 9/9/2005. Claim 1 has been amended. Claims 1-3 and 5-10 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. This action is **FINAL.**

Priority

Acknowledgement of claim to foreign priority of Japanese Application, 11/268745, filed 9/22/1999 under 35 U.S.C. 119(a)-(d) has been made and the certified copy was received 2/4/2005.

Response to Arguments

Applicant's arguments with respect to claims 1-3 and 5-10 have been considered but are moot in view of the new ground(s) of rejection below.

THE FOLLOWING ARE NEW REJECTIONS NECESSITATED BY APPLICANT'S AMENDMENTS TO THE CLAIMS

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless–

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-3 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Livak et al.(*PCR Methods and Applications* 4:357-362, 1995).

With regard to claim 1, Livak et al. teach a probe comprising a nucleic acid carrying a labeling substance that releases energy and an energy-absorbing substance absorbing the energy(quencher) which is capable of specifically binding to a double-stranded nucleic acid, wherein the labeling substance is positioned on the nucleic acid 0 to 1 nucleotides apart from the energy-absorbing substance wherein the energy absorbing substance is capable of absorbing the energy released from the labeling substance, wherein the energy-absorbing substance specifically interacts with the double stranded nucleic acid due to the hybridization of the probe with a target nucleic acid thereby resulting in no quenching of the labeling substance. Specifically the reference teaches on page 359 in figure 2 for example the probe "A1-2" that has the fluorophore and quencher separated by a single nucleotide(0-1).

With regard to claim 2, the energy of the probe is photo energy as produced by a fluorescein reporter(see page 359 results section for example).

With regard to claim 3, the labeling substance is selected from the group consisting of a fluorescent substance, a delayed fluorescent substance, and a chemiluminescent substance. As referred to above, the substance is fluorescein, a fluorescent substrate.

With regard to claim 7, a solid phase carrier for detecting a nucleic acid, on which the probe of claim 1 is immobilized on a Sephadex column as can be seen on the left hand side of page 358.

With regard to claims 8 and 9, as stated above, Livak et al. teach the fluorescence detection via a Perkin-Elmer Taq Man LS-50B System, which measures emission with a 485nm excitation filter. On page 359, the reference teaches that "these probes hybridize to a target sequence in the human *B-actin* gene.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 5, 6, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Livak et al.(*PCR Methods and Applications* 4:357-362, 1995) as applied to claims 1-3 and 7-9 above, and further in view of Livak et al.(US Patent 5,723,591).

With regard to claim 1, Livak et al.(*PCR Methods and Applications* 4:357-362, 1995) teach a probe comprising a nucleic acid carrying a labeling substance that releases energy and an energy-absorbing substance absorbing the energy(quencher) which is capable of specifically binding to a double-stranded nucleic acid, wherein the labeling substance is positioned on the nucleic acid 0 to 1 nucleotides apart from the energy-absorbing substance wherein the energy absorbing substance is capable of absorbing the energy released from the labeling substance, wherein the energy-absorbing substance specifically interacts with the double stranded nucleic acid due to the hybridization of the probe with a target nucleic acid thereby resulting in no quenching of the labeling substance. Specifically the reference teaches on page 359 in figure 2

for example the probe "A1-2" that has the fluorophore and quencher separated by a single nucleotide(0-1).

With regard to claim 2, the energy of the probe is photo energy as produced by a fluorescein reporter(see page 359 results section for example).

With regard to claim 3, the labeling substance is selected from the group consisting of a fluorescent substance, a delayed fluorescent substance, and a chemiluminescent substance. As referred to above, the substance is fluorescein, a fluorescent substrate.

With regard to claim 7, a solid phase carrier for detecting a nucleic acid, on which the probe of claim 1 is immobilized on a Sephadex column as can be seen on the left hand side of page 358.

With regard to claims 8 and 9, as stated above, Livak et al. teach the fluorescence detection via a Perkin-Elmer Taq Man LS-50B System, which measures emission with a 485nm excitation filter. On page 359, the reference teaches that "these probes hybridize to a target sequence in the human *B-actin* gene.

However, the *PCR Methods and Applications* 4:357-362, 1995 Livak reference does not teach the use of an intercalating probe or an energy absorbing substance selected from the group consisting of pyrene, coumarin, and acridine.

But the Livak et al. reference of (US Patent 5,723,591) teaches with regard to claim 5 and claim 10, that the energy absorbing(quencher) is an intercalator or a substance which specifically binds to a double stranded nucleic acid, in Col. 11 in their teachings of exemplary reporter-quencher pairs and dyes including acridines like acridine orange, "pyrenes and the like"(lines 33-35).

With regard to claim 6, Livak et al. teach that the labeling substance "may be selected from xanthene dyes, including fluoresceins, and rhodamine dyes"(Col. 11 lines 22-23). While Livak et al. also teach that the energy absorbing(quencher) may be selected from another group of fluorescent compounds including acridines like acridine orange, "pyrenes and the like"(lines 33-35).

Therefore, it would have been *prima facie* obvious for one of skill in the art at the time the invention was made to have included the particular fluorophores and quenchers used in the Livak et al. patent since in Col. 11 lines 22-35 the patent teaches that "exemplary reporter-quencher pairs may be selected from such choices such as...acridines" and further the many references listed in Col 11 lines 36-61 teach the successful use of such combinations as well.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3 and 5-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir.

1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of the invention. Claims 1-3 and 5-10 are broadly drawn to a probe comprising a nucleic acid carrying a labeling substance that releases energy and an energy-absorbing substance which is capable of specifically binding to a double-stranded nucleic acid, wherein the labeling substance is positioned on the nucleic acid 0 to 1 nucleotides apart from the energy absorbing substance. The specification does not at all enable the ability of the two dyes to function in such a close proximity to one another. More specifically it is unclear how the probe could be cleaved between an adjacent quencher and fluorophore in order for the fluorophore to avoid being quenched. On page 13 in table 1 of the specification, No. 13, EFN1-FP with no nonlabeled oligonucleotide yielded a fluorescent intensity of only 156, whereas sample 14 yielded a fluorescent intensity of 661 and No. 15 yielded 160. It is unclear which of the figures are or are not significant considering there is no scale or figures that describe the actual, detectable fluorescence. The specification does not teach how the non-quenching occurs with the two labels so close to one another.

Scope of the invention. The scope of the invention is very broad, claiming all probes consisting minimally of any two labels one releasing energy and the other absorbing it. Much unpredictability exists in the broad claiming of any product that the art teaches in the past to be unsuccessfully used.

State of the art. The prior art does not disclose a probe where the fluorophore is located 0-1 nucleotides apart from the quenching moiety that is functional in not quenching. The prior art Livak et al.(*PCR Methods and Applications* 4:357-362, 1995), teaches that a series of probes with increasing distances between the fluorescein reporter and rhodamine quencher were tested to investigate the minimum and maximum spacing that would give an acceptable performance in the 5' nuclease PCR assay. The prior art, then teaches a probe, "A1-2", that has a ΔRQ value that is close to zero, indicating that the probe was not cleaved appreciably during the amplification reaction. The art then suggests that "with the quencher dye on the second nucleotide from the 5'end, there is insufficient room for Taq polymerase to cleave efficiently between the reporter and the quencher"(Pg. 359). In addition, the art teaches that there are three main factors that determine the performance of a double labeled fluorescent probe in the 5' nuclease PCR assay(Pg. 360 far right hand side). The first is the degree of quenching observed in the intact probe. This is characterized by the value of RQ-, which is the ratio of the reporter to the quencher fluorescent emissions for a no template control PCR. Influences on the value of RQ- included the particular reporter and quencher dyes used. Spacing between reporter and quencher dyes, nucleotide sequence context effects, presence of structure or other factors that reduce flexibility of the oligonucleotide, and the purity of the probe. In contrast, the present specification provides no guidance as to these factors or any other data as to the significance of their figures in Table 1.

Number of working examples and Guidance provided by applicant. The instant specification only provides the "fluorescent intensity" result for any number of labeled oligonucleotides in table 1. Considering the unpredictability surrounding the lack of those

details commonly used in the art to classify the performance of double labeled probes as pointed out in the State of the art section of this rejection, the skilled artisan would have to practice undue and unpredictable trial and error experimentation in order to practice the invention with the quencher and fluorophore moieties located within 0-1nucleotides of one another.

Level of skill in the art. The level of skill involved is very high if not impossible. Additionally, the functional use of such assumed similar properties from such different molecules(where the two labels are located in a different distance at 6 or 16 nt apart for instance, is seen, in this instance, to be prophetic.

Unpredictability of the art. There are examples of double labeled probes in the art that are not able to fluoresce upon target hybridization. Specifically, these examples are for the presently claimed double-labeled probes wherein the fluorophore and quencher are located at 0-1 nucleotides apart. The specification provides no examples and data showing the successful use of such probes either. In light of these deficiencies, the skilled artisan would be forced to practice undue and unpredictable trial and error experimentation when practicing the instant invention.

Considering the Nature of the invention, the guidance provided by both the prior art and the instant specification, and the broad scope of the invention, it is clear that the skilled artisan would be required to practice undue and unpredictable trial and error experimentation to practice the invention that is claimed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A. Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris
12/7/2005

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600